Revised Sequence Listing

A revised sequence listing is submitted herewith. The nucleotide and amino acid sequences of SEQ ID NO:4 and the amino acid sequence of SEQ ID NO:5 have been amended as indicated in Table I below. The sequence information for SEQ ID NO:4, as originally filed, referenced Winkelmann et al., Blood, 1990, 76(1):24-30; Jones et al., Blood, 1990, 76(1):31-35; and Noguchi et al., Blood, 1991, 78(10):2548-2556, for publication information of the human EPO-R sequence. A comparison of the nucleotide and amino acid sequences of the human EPO-receptor disclosed in these papers, however, indicates that there are eight nucleotide differences (nucleotides 304, 305, 565, 567, 568, 730, 731, and 1449) and four amino acid differences (amino acids 102, 189, 190, and 244) between Winkelmann et al., and the Jones et al. and Noguchi et al. papers.

TABLE I

Changes to EPO-R Sequence

Nucleotide				Amino Acid		
Position	Submitted	Revised	Codon as Revised	Position	Submitted	Revised
304	G	C	CGG	102	Ala	Arg
305	C	G	CGG	102	Ala	Arg
565	G	C	CGG	189	Gly	Arg
567	C	G	CGG	189	Gly	Arg
568	G	C	CCA	189	Ala	Pro
662	T	G	CGC	221	Leu	Arg
730	A	G	GAG	244	Thr	Glu
731	C	A	GAG	244	Thr	Glu
1449	C	G	GGG	483	Gly	--*

* = no change

As indicated in the specification at page 13, line 21 through page 14, line 2, LAP37, a full-length human EPO-R cDNA preparation was provided by Dr. Bernard Forget of Yale University. The nucleotide sequence of this cDNA is provided in the Winkelmann et al. publication referenced above, in which Laura A. Penny (LAP) and Bernard Forget are co-

authors. Thus, the nucleotide and amino acid sequences of the clone which was used in the present application are the same as the sequences disclosed by Winkelmann et al.

An additional change to SEQ ID NO:4 was introduced at nucleotide 662, with the corresponding change introduced at amino acid 221. This revision is due to a typographical error. SEQ ID NO:4, as originally submitted on January 30, 1998, indicated that nucleotide 662 was a "G". In the sequence listing of January 11, 1999, however, this position was inadvertently changed to a "T". Furthermore, a comparison of the sequences in the three publications referenced above indicates that they each contain a "G" at nucleotide 662. The change from a "T" to a "G" at this position results in substitution of an arginine for leucine at amino acid 221.

The Examiner is respectfully requested to enter the new sequence listing. No new matter is introduced by the changes to SEQ ID NO:4 and SEQ ID NO:5.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 3 and 5 under 35 U.S.C. §112, first paragraph. The Examiner asserted that "[t]he specification as filed does not support the recitation of unglycosylated EPO receptor polypeptides. The subgenus of such unglycosylated receptors is not necessarily the same as any of the subgenera which are described in the specification. It would be possible, for example, to produce the specified polypeptides in expression systems not capable of glycosylating them but yet capable of effecting other posttranslational modifications." Applicant respectfully traverses.

Applicant indicated in the previous response that one of ordinary skill in the art would have appreciated that a prokaryotically expressed polypeptide does not contain post-translational modifications such as glycosylation. The nonglycosylated nature of the polypeptide is a feature that is inherent to production of proteins in prokaryotes. Thus, recitation of the phrase "wherein said polypeptide is nonglycosylated" is supported by the application, as originally filed.

Applicant has exemplified the production of a purified, non-glycosylated human erythropoietin receptor polypeptide consisting of about amino acid 25 to about amino acid 250 of the full length human erythropoietin receptor protein of SEQ ID NO:5, wherein the human erythropoietin receptor polypeptide is capable of binding human erythropoietin. The claimed

polypeptide was produced in *E. coli*, and the specification describes the materials which were used, the construction of necessary vectors, and purification of the polypeptide. See, specification, pages 13-26. Thus, the specification enables the production of the claimed polypeptide.

In view of the above remarks, the Examiner is requested to withdraw the rejection of claims 3 and 5 under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §102(b)

The Examiner rejected claims 3 and 5 under 35 U.S.C. §102(b) as being anticipated by Harris et al., J. Biol. Chem., 1992, 267:15205-15209. The Examiner asserted that "Harris describes the production of an unglycosylated hEPO-R polypeptide, an EREx fusion produced in *E. coli* and that it binds to immobilized hEPO." The Examiner also asserted that "[i]t reasonably appears that the prior art EREx polypeptide meets the limitation of "consisting essentially of" the extracellular domain of the EPO receptor, and it further reasonably appears that notwithstanding its use for binding assays which do not employ an immunochemical reagent, the GSH-agarose-immobilized EREx polypeptide meets all the material and functional limitations of the "immunoassay reagent" of claim 5." Applicant respectfully traverses.

As indicated by the Examiner under point 5 of the Office Action, "Harris does not describe the production of a polypeptide consisting of only the extracellular domain of hEPO-R as an immunogen, nor does it describe solid-phase assays employing the antibodies it discloses." Thus, the hEPO-R fusion polypeptide of Harris et al. does not meet the limitations of amended claim 3, which recites a purified EPO receptor polypeptide consisting of about amino acid 25 to about amino acid 250 of the full length human erythropoietin receptor protein of SEQ ID NO:5, wherein the receptor is capable of binding human erythropoietin, and wherein the polypeptide is non-glycosylated. The Examiner is requested to withdraw the rejection of claims 3 and 5 under 35 U.S.C. §102(b).

Rejection under 35 U.S.C. §103

The Examiner indicated that claims 4, 6, and 8 were rejected under 35 U.S.C. §103(a) as being unpatentable over Harris et al. in view of D'Andrea et al. (U.S. Patent No.

5,378,808). Applicant believes the Examiner is referring to claims 3 and 5 of the present application.

Harris et al. is described above. The Examiner asserted that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to produce a secreted receptor polypeptide according to the teachings of D'Andrea using an *E. coli* expression system, as described by Harris, because the artisan would reasonably have expected such a polypeptide to have the EPO-binding properties of the ERExfusion protein as described by Harris and to be useful for any of the other purposes described in the '808 patent."

As described above, Harris et al. do not teach or suggest a purified EPO receptor polypeptide consisting of about amino acid 25 to about amino acid 250 of the full length human erythropoietin receptor protein of SEQ ID NO:5.

D'Andrea et al. do not remedy the deficiencies of Harris et al. D'Andrea et al. do not disclose production of a nonglycosylated human EPO-R polypeptide. Furthermore, the purified EPO-R polypeptide of D'Andrea et al. has an amino acid sequence that differs from that of the presently claimed purified EPO-R polypeptide. Residues 102, 189, 190, and 244 of the D'Andrea et al. hEPO-R polypeptide differ from the amino acid sequence of SEQ ID NO:5. Thus, the combination of Harris et al. and D'Andrea et al. does not render the claimed inventions obvious. The Examiner is requested to withdraw the rejection of claims 3 and 5 under 35 U.S.C. §103.

Applicant submits that all claims are now in condition for allowance, which action is requested. The Examiner is invited to telephone the undersigned if it is felt that such would advance prosecution of the application.

Please charge any additional fees, or make any credits, to Deposit Account No. 06-1050.

Respectfully submitted,

Date: August 16, 1999

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